Proton-pump inhibitors for the treatment of functional dyspepsia

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Abstract: In the Rome III classification, functional dyspepsia (FD) has been further subcategorized into two different syndromes, namely, epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). Acid-related pathophysiology seems to be mainly responsible for EPS, and antisecretory agents such as proton-pump inhibitors (PPIs) seem to be effective mainly against EPS. However, recent information as to the relationship between initial duodenal acid sensitization in the early postprandial phase and delayed gastric emptying in the later postprandial phase would suggest the amelioration of PDS by antisecretory agents. In the present review, we summarized the recent literature on the direct and indirect effect of PPIs in FD (including not only Rome III, but also Rome II criteria). The effects of PPIs against FD are heterogeneous, depending on the protocol of the clinical studies, and the inclusion criteria of each randomized controlled trial (primary care or tertiary care population). As the placebo effects cannot be ignored in this disease, a placebo-controlled study would be necessary, at least for the evaluation of the effect of each agent on symptom relief in patients with FD. Further studies directly comparing PPIs with suitable placebos in terms of their effects in reducing the symptoms of endoscopically confirmed, Rome III-based FD are awaited.

Keywords: antisecretory agents, functional gastrointestinal disorders, *Helicobacter pylori*, randomized controlled study, uninvestigated dyspepsia

Introduction

Many patients with functional gastrointestinal disorders (FGIDs) have chronic symptoms pertaining to the gastroduodenal region. The Rome III consensus, which is based on the consensus opinion of an international panel of clinical investigators who reviewed the available evidence, proposed a classification of functional gastroduodenal disorders [Suzuki *et al.* 2006; Tack *et al.* 2006]. Among four categories of functional gastroduodenal disorders, the first category is functional dyspepsia (FD), associated with symptoms thought to originate from the gastroduodenal region, specifically manifesting as one or more of the four main symptoms of epigastric pain or burning, postprandial fullness, and early satiety. Furthermore, FD has been further subclassified into postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). This Rome III classification requires further research and careful validation; however, the criteria appear to be of value in clinical practice, for epidemiological, pathophysiological, and

clinical management studies, and for drug development.

Gastric acid secretion and the perceived sensation associated with it are among the potentially important players in the genesis of dyspeptic symptoms. In patients with FD, especially those with EPS, suppression of gastric acid secretion by antisecretory agents such as proton-pump inhibitors (PPIs) or histamine type 2-receptor antagonists (H_2 blocker) seems to ameliorate the epigastric pain or burning. Furthermore, even in PDS, as the initial gastric acid emptying may play a pathogenetic role on symptom generation through the early onset of duodenal brake, acid suppression might be effective, at least in part, against the bothersome postprandial fullness [Grudell *et al.* 2006].

PPIs are among the strongest of drugs available for gastric acid suppression. In the CADET-HN study [Veldhuyzen van Zanten *et al.* 2005], the effect of omeprazole to dyspepsia symptoms

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was evaluated. *Helicobacter pylori*-negative patients recruited with dyspepsia symptoms of at least moderate severity were randomized to a 4-week treatment protocol of omeprazole 20 mg o.d. or placebo, followed by on-demand therapy for an additional 5 months. Those who participated in this study were not previously investigated FD patients, but the success rate (no complete disappearance or minimal residual symptoms) of the omeprazole group at 4 weeks was 51% ($N=69/135$, 95% CI 43–60%) and were significantly superior to the placebo group (23%, $N=31/133$, 95% CI 16–31%, $p < 0.05$). Furthermore, the proportion of patients who were responders at 4 weeks and at 6 months was significantly greater among those receiving omeprazole (31%, $N=42/135$, 95% CI 23–39%) than placebo (14%, $N=18/133$, 95% CI 8–20%, $p = 0.001$). These results may suggest that treatment with omeprazole provides superior symptomatic relief as compared with placebo in the treatment of *H. pylori*-negative primary care uninvestigated dyspepsia patients.

Review methodology of articles concerning PPIs on functional dyspepsia

A literature search of PubMed was performed using the keywords “functional dyspepsia”, “nonulcer dyspepsia”, and “proton-pump inhibitor”, and was limited to studies published in the English language over the past 14 years (1997–2010) and to human studies (meta-analyses, randomized-controlled trials (RCTs),

clinical trials, comparative studies, and systemic reviews). After compiling a list of the 79 studies identified, 46 publications not directly linked to FD and PPIs (but concerning mainly *H. pylori* eradication therapy [Suzuki *et al.* 2007]) were excluded. Furthermore, three articles which have only simple abstracts without details were also excluded.

Of the remaining 30 studies, 1 study dealing with only acid-related dyspepsia which seems to overlap with gastroesophageal reflux disease (GERD), 4 descriptive reviews of other studies, and 11 manuscripts not concerned with PPI therapy on FD were further excluded. Finally, 14 articles including 4 systematic reviews, 7 RCTs, and 3 non-RCTs were reviewed in detail (Figure 1), and the results are presented here.

Results of the literature review

Randomized controlled trials. The results of five RCTs [Grudell *et al.* 2006; Van Zanten *et al.* 2006; Peura *et al.* 2004; Wong *et al.* 2002; Talley *et al.* 1998] on the efficiency of PPIs in functional dyspepsia are shown in Table 1.

First, Talley and colleagues conducted an RCT to evaluate the efficacy of omeprazole in patients with FD [Talley *et al.* 1998]. Patients ($n = 1262$, mean age 41–43) with a clinical diagnosis of FD were enrolled in their study. The participant patients had a history of persistent or recurrent

Figure 1. Literature selection flow. DB, database; FD, functional dyspepsia; PPI, proton-pump inhibitor.

epigastric pain or discomfort for at least 1 month, and the symptoms were perceived on at least 25% of the days of the month, with negative findings on esophagogastroduodenoscopy (EGD). Patients were randomized to receive omeprazole 20 or 10 mg, or identical placebo, for 4 weeks. On an intention-to-treat (ITT) analysis ($n=1248$), complete symptom relief was observed in 38% of the patients on omeprazole 20 mg, as compared with 36% of patients on omeprazole 10 mg and 28% of the patients on placebo ($p=0.002$ and 0.02 , respectively). In addition, the patients were classified into three subgroups based on the type of the symptoms: ulcer-like dyspepsia, reflux-like dyspepsia, and dysmotility-like dyspepsia. The symptom relief was compared among these patient groups. Complete relief was obtained in 40% and 54% of patients with ulcer-like dyspepsia and reflux-like dyspepsia, respectively, on omeprazole 20 mg, and in 35% and 45% of patients with ulcer-like dyspepsia and reflux-like dyspepsia, respectively, on omeprazole 10 mg, as compared with in 27% and 23% of the above two respective patient groups on placebo treatment (all $p < 0.05$, except omeprazole 10 mg in ulcer-like dyspepsia, $p=0.08$). On the other hand, there was no significant benefit of omeprazole over placebo in the group with dysmotility-like dyspepsia. The results suggest that symptom subgrouping based on symptom predominance has clinical utility because it predicts treatment response.

Wong and colleagues examined the effect of different doses of lansoprazole for the treatment of

FD in Chinese patients [Wong *et al.* 2002]. A total of 453 patients with a clinical diagnosis of FD according to the Rome II criteria and normal EGD were randomized to receive lansoprazole 30 mg, lansoprazole 15 mg, or placebo, for 4 weeks. Dyspepsia symptom scores and quality of life (QOL; using SF-36 score) were evaluated before and after 4 weeks treatment. There was no difference in the proportion of patients with complete symptom relief in the lansoprazole 30 mg (23%, $N=35/149$, 95% CI 17–30%) and lansoprazole 15 mg (23%, $N=35/152$, 95% CI 17–30%) groups as compared with that in the placebo group (30%, $N=45/152$, 95% CI 23–37%). Furthermore, the mean dyspepsia scores of the three groups were further improved after 4 weeks ($p < 0.001$). This result means that there were no significant differences among these groups in terms of the QOL.

In contrast to the above findings, according to the study conducted by Peura and colleagues, in which 921 patients were assigned randomly to receive lansoprazole 30 mg, lansoprazole 15 mg, or placebo for 8 weeks, a significant reduction in the percentage of days with upper abdominal discomfort was observed for patients treated with lansoprazole 30 mg (34%) or 15 mg (35%), but not for those treated with placebo (19%) ($p < 0.001$) [Peura *et al.* 2004]. Similarly, a larger percentage of patients treated with lansoprazole 30 mg (44%) or 15 mg (44%) reported complete symptom resolution (defined as no episodes of upper abdominal discomfort during the 3 days prior to the study visit) than in the group treated with placebo (29%) ($p < 0.001$). In their

Table 1. Randomized controlled trials.

Study	<i>n</i>	Drug	Dosage	Subjects	Outcome	Period	Effect
Talley <i>et al.</i> [1998]	1248	Omeprazole	20 mg/10 mg/ placebo	With normal EGD; epigastric pain or discomfort	Symptom relief at interview	4 weeks	Effective
Wong <i>et al.</i> [2002]	453	Lansoprazole	30 mg/15 mg/ placebo	With normal EGD; clinical diagnosis of FD	Dyspepsia symptom score Quality of life (SF-36 score)	4 weeks	Ineffective
Peura <i>et al.</i> [2004]	921	lansoprazole	30 mg/15 mg/ placebo	With normal EGD; predominant upper abdominal discomfort	Symptom relief	8 weeks	Effective
Van Zanten <i>et al.</i> [2006]	224	Esomeprazole	40 mg/ placebo	With normal EGD; moderate severity of symptom (GOS scale)	Symptom relief (GOS ≤ 2)	4 weeks 8 weeks	Effective Ineffective

n, number of patients; EGD, esophagogastroduodenoscopy; SPECT, single photon emission computed tomography; GOS scale, Global Overall Symptom scale

study, however, improvement of upper abdominal discomfort was seen only in patients who had at least some symptoms of heartburn at enrollment. They concluded that lansoprazole was significantly better than placebo in reducing the symptom of persistent or recurrent upper abdominal discomfort associated at least with some heartburn. The fact that about 75% of the enrolled patients had some symptom of heartburn in spite of excluding patients with predominant symptoms of GERD indicated that it was not only a characteristic symptom of gastroesophageal reflux. The presence of some degree of heartburn may be a marker of acid sensitivity and a useful predictor of response to PPIs, indicating that there was no difference in the effects of the groups receiving the 30 mg dose and 15 mg dose. The effect of PPI on FD may not be dependent on the dose and this may be related to the mechanism of FD.

Concerning esomeprazole, Van Zanten and colleagues designed an RCT in which 224 adult patients who had dyspepsia symptoms of at least moderate severity and no findings on EGD were enrolled [Van Zanten *et al.* 2006]. The subjects were randomized to receive esomeprazole 40 mg or placebo once daily for 8 weeks. With regards to the primary outcome measure of symptom relief at 8 weeks, there was no statistically significant difference between the esomeprazole 40 mg (55.1%, $N=60/109$, 95% CI 45.2–64.6) and placebo (46.1%, $N=53/115$, 95% CI 36.8–55.6) once daily groups ($p=0.16$), although at 4 weeks esomeprazole provided significantly greater symptom relief (50.5%, $N=55/109$, 95% CI 40.7–60.2) than placebo (32.2%, $N=37/115$, 95% CI 23.8–41.5) ($p=0.009$). The difference in therapeutic gain between 4 and 8 weeks was considered to be largely attributable to the higher placebo response rate at 8 weeks.

Randomized-controlled trials not concerned directly with the efficacy of PPIs against functional dyspepsia. FD patients have been demonstrated to have enhanced visceroperception and a decreased duodenal motor response to intraduodenal acid infusion. Schwartz and colleagues conducted antropyloroduodenal manometry before and after the treatment in patients randomly assigned to receive treatment with pantoprazole ($n=10$) or placebo ($n=9$) for 2 weeks, and showed that pantoprazole decreased the duodenal acid hypersensitivity to

some extent ($p=0.07$), but did not improve the impaired duodenal motor response [Schwartz *et al.* 2001].

On the other hand, Bolling-Sternevald and colleagues investigated the factors predictive of a good response to PPIs [Bolling-Sternevald *et al.* 2003]. Patients ($n=826$) with FD who were treated with omeprazole 10 or 20 mg or placebo for 4 weeks were collected from another RCT [Talley *et al.* 1998]. Fewer days with symptoms during the first week was associated with a higher response rate at 4 weeks ($p<0.0001$), suggesting that the initial response to PPIs could predict the subsequent response. The most discriminating predictor of treatment success was the number of days with epigastric pain/discomfort during the first week of treatment ($p<0.0001$). In addition, age >40 years ($p=0.03$), bothersome heartburn ($p=0.003$), low scores for bloating ($p=0.006$), epigastric pain ($p=0.02$), and diarrhea ($p=0.03$), history of symptoms for <3 months ($p=0.009$) and low impairment of vitality ($p=0.03$) at baseline were identified as positive predictors of the outcome.

Symptom relapse after PPI treatment in patients with FD is another important issue that needs to be discussed. Reimer and colleagues [Reimer and Bytzer, 2010] investigated the effects of a PPI against symptom relapse in the absence of abnormal endoscopic findings. A total of 31 patients were randomized to 7 days of esomeprazole 40 mg or placebo. Successful effect of therapy after 7 days was observed in 12 of 15 patients (80%) in the esomeprazole group *versus* 2 of 16 (13%) in the placebo group ($p<0.001$), suggesting that short-term esomeprazole therapy was superior to placebo in patients with recurrence of symptoms not associated with abnormalities on endoscopy. They showed on the other RCT that PPI therapy for 8 weeks induced acid-related symptoms in healthy persons after withdrawal [Reimer *et al.* 2009]. The 44% ($N=26/59$) of those randomized to 8 weeks of esomeprazole 40 mg/day followed by 4 weeks with placebo reported acid-related symptom in weeks 9–12 compared with 15% ($N=9/59$; $p<0.001$) in the placebo group, indicating that this phenomenon was caused by rebound acid hypersecretion (RAHS).

Nonrandomized studies. There were three non-RCTs (Table 2), as described in the following; for

Table 2. Nonrandomized controlled studies.

Author	Year	n	Drug	Dosage	Subjects	Outcome	Period	Effect
Mundo-Gallardo <i>et al.</i>	[2000]	189	Rabeprazole	20 mg	With normal EGD; functional dyspepsia	Symptom relief	4 weeks	Effective
Ghosh <i>et al.</i>	[2008]	46	Rabeto plus (rabeprazole + itopride)	1 capsule	Functional dyspepsia overlapped with NERD	Symptom relief global assessment of efficacy and tolerability	4 weeks	Effective
Miyamoto <i>et al.</i>	[2010]	467	Rabeprazole lansoprazole omeprazole + mosapride citrate (prokinetics)	10 mg 30 mg/ 15 mg 20 mg/ 10 mg 5 mg	GERD (NERD + RE)	Total score/ reflux score/ dyspeptic score in FSSG	2 weeks + 4 weeks	Effective

n, number of patients; EGD, esophagogastroduodenoscopy; NERD, nonerosive reflux disease; GERD, gastroesophageal reflux disease; RE, reflux esophagitis

two of these, only the abstract could be referred [Ghosh *et al.* 2008; Mundo-Gallardo *et al.* 2000].

Ghosh and colleagues indicated the efficiency of a fixed-dose combination (FDC) of rabeprazole and itopride [a prokinetic (PK) agent] in the management of FD [Ghosh *et al.* 2008]. They designed an open, prospective, noncomparative, multidose study; a total of 46 adult patients with FD [overlapped with non-erosive reflux disease (NERD)] were given one capsule of the rabeto plus formulation (FDC) for 4 weeks, and completed the study. Most patients showed near total symptom relief by the end of the study period and response to the drug was reported as excellent or good by 93% of the patients and their treating physicians.

Mundo-Gallardo and colleagues investigated the effect of rabeprazole on FD in a multicenter, open-label study [Mundo-Gallardo *et al.* 2000]. They assessed the clinical efficacy and tolerability of rabeprazole 20 mg in 189 patients with FD. The clinical efficacy rate was 86% after only 4 weeks of treatment, and the symptom control was remained until the end of 4 weeks without treatment.

In the Rome III criteria, overlap between FD and NERD is recognized. Miyamoto and colleagues designed a study to investigate the effects of treatment in patients with NERD and RE: factors predictive of a poor response to PPIs and also the effects of PKs were evaluated [Miyamoto *et al.* 2010]. The subjects were 467 GERD

patients (NERD 349, RE 118). PPI treatment (rabeprazole 10 mg: $n = 214$; lansoprazole 30 mg: $n = 97$; lansoprazole 15 mg: $n = 63$; omeprazole 20 mg: $n = 54$; omeprazole 10 mg: $n = 39$) was administered for 2 weeks. The total score (TS) for symptoms, the reflux score (RS), and the dyspeptic score (DS) were assessed using the frequency scale for the symptoms of GERD (FSSG). There was higher tendency towards nonresponse to PPI treatment among the patients with NERD (52.7%, 184/349) than among those with RE (42.4%, 50/118) ($p = 0.0516$). In NERD, younger age ($p = 0.0066$), presence of constipation ($p = 0.0014$), higher TS ($p = 0.0177$), DS ($p = 0.0012$) and scores for the four items of FSSG (bloated stomach: $p = 0.01547$; heavy stomach: $p = 0.0009$; sick feeling after meal: $p = 0.0297$; and early satiety during a meal: $p = 0.0004$) were associated with a poor response to PPIs. In addition, PKs were added to PPI for another 4 weeks in NERD patients nonresponsive to PPIs. Significant improvement of the TS (pretreatment: 17.4 ± 7.7 versus PPI only after 2 weeks 14.6 ± 6.0 versus PPI + PK after 6 weeks 7.7 ± 5.2 , $p < 0.0001$) was observed in the nonresponders to PPIs among the NERD patients after the addition of PKs (mosapride citrate 5 mg t.i.d., a selective 5-HT₄ receptor agonist, stimulates upper gastrointestinal motor activity, and is free of dopamine D₂ receptor antagonist properties).

Systematic reviews. There were five systematic reviews [Sanaka *et al.* 2010; Kleibeuker and

Theijs, 2004; Moayyedi *et al.* 2004; Talley and Lauritsen, 2002; Chiba *et al.* 2000].

Moayyedi and colleagues conducted a systematic review of eight RCTs conducted to evaluate the effect of PPI therapy in patients with nonulcer dyspepsia ($n=3293$, including five trials of omeprazole and three of lansoprazole), identified through a search of articles published in MEDLINE, EMBASE/Excerpta, Medica, Cochrane-Controlled Trials Register, CINAHL, and SIGLE until September 2002 [Moayyedi *et al.* 2004]. The relative risk of residual dyspepsia symptoms following PPI therapy *versus* placebo was 0.86 (95% CI, 0.78–0.95; $p=0.003$), with a number needed to treat of 9 (95% CI 5–25). On the other hand, from an economic standpoint, the PPI strategy (PPI price, US\$90/month, evaluated over a 1-year period) would cost an additional US\$278/month for freedom from dyspepsia than over-the-counter (OTC) antacid therapy at US\$57/month (OTC price US\$ 19.99). However, since the monthly cost of PPI would fall each year, the updated calculation for FD management should be performed.

Talley and Lauritsen summarized the data of BOND and OPERA [Talley *et al.* 1998], PILOT, and a 3-month follow up study, ENCORE, and indicated that omeprazole 20 or 10 mg may be superior to placebo for obtaining relief from FD symptoms [Talley and Lauritsen, 2002]. Pooling the BOND and OPERA trials, complete relief of symptoms was achieved in 38.2% of the 20 mg omeprazole group ($p=0.002$) and in 36.0% of the 10 mg omeprazole group ($p=0.02$) compared with 28.2% in the placebo group. In patients with ulcer-like and reflux-like dyspepsia, complete relief of symptoms was achieved in 40% and 54% of the 20 mg omeprazole group ($p=0.05$) and in 35% and 45% of the 10 mg omeprazole group ($p=0.08$ and $p=0.05$, respectively) compared with 27% and 23% in the placebo group in pooled analysis. In addition, these trials showed that symptom relief may be unrelated to the *H. pylori* status, and that successful treatment may have a positive impact on the patient QOL assessed over a 3-month period after treatment cessation. Compared with patients in whom symptoms still persisted at the end of trial, patients with complete absence of symptoms at the end of active or placebo treatment had fewer days on medication (9.2 *versus* 22.7, $p<0.001$), fewer clinical visits (1.5 *versus* 2.0, $p<0.001$) and

the psychological general well being index ($p<0.001$).

Another review [Kleibeuker and Theijs, 2004], based on the examination of several trials, indicated the efficacy of PPIs in the treatment of FD (RR reduction of 14%), and that the best predictor of a beneficial effect was the response during the first week of treatment. Additional predictors included a history of symptoms of less than 3 months duration and a history of bothersome heartburn [Peura *et al.* 2004; Bolling-Sternevald *et al.* 2003]. They pointed out that PPIs provide only a small beneficial effect in FD patients, and that this effect is largely attributable to a reduction in gastroesophageal reflux-induced complaints. They emphasized that the response during the first week of PPI therapy can probably be used as an indicator to decide on whether or not to continue using the drug for treatment.

On the other hand, Sanaka and colleagues reviewed several studies (1979–2009) that investigated the rate of gastric emptying [Sanaka *et al.* 2010]. They suggested that PPIs (omeprazole and lansoprazole, but not rabeprazole) delayed the gastric emptying of solid meals, while having variable effects on gastric liquid emptying. They hypothesized that PPIs impair hydrolytic digestion by inhibiting acid-dependent peptic activity, thereby delaying the gastric emptying rate of solids, while the gastric emptying rate of liquids largely depends on the volume and energy density of the intragastric contents. PPIs variably modify the volume and energy density by reducing gastric fluid secretion, thereby modifying the rate of gastric emptying of liquids in an unpredictable manner.

Summary

Taken together with the abovementioned information in relation to PPI efficacy against the symptoms of FD, the placebo effect, which is approximately 30–40% among patients in RCTs, cannot be ignored in patients with FD [Moayyedi *et al.* 2004]. The placebo response may, in part, reflect the natural fluctuations of upper gastrointestinal tract-originated symptoms, although this is not the only likely factor [Thompson, 2000]. According to a recent report by Talley and colleagues, independent predictors of a weak placebo response were a lower BMI and a more consistent predominant symptom pattern (both $p<0.05$), while no association was seen with the age, gender, center type,

baseline symptom score, baseline rate or change in rate of gastric emptying, or the baseline QOL [Talley *et al.* 2006]. Their data indicated that aside from BMI and a consistent predominant symptom pattern, the aforementioned factors (symptom severity, age, gender, center type and rate of gastric emptying) were not useful predictors of a placebo response [Talley *et al.* 2006]. As shown in the previous studies, the placebo effects cannot be ignored in the field of FGIDs; a placebo-controlled study would be necessary, at least for the efficacy evaluation of each treatment agent on the symptoms of FD. Further studies directly comparing PPIs with suitable placebos in terms of their effects in reducing the symptoms of endoscopically confirmed, Rome III-based FD are awaited.

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Conflict of interest statement

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